FOCUS ON PSORIASIS: A REPORT FROM THE 73RD ANNUAL MEETING OF THE AMERICAN ACADEMY OF DERMATOLOGY

Psoriasis-related topics included targeted therapies, safety of biologics, comorbidities

By Jessica M. Donigan, MD

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Psoriasis and its comorbidities were the focus of several of the sessions at the 73rd annual meeting of the American Academy of Dermatology (AAD) held in San Francisco, Calif., in March 2015. Following is a summary of the key aspects discussed.

New psoriasis therapies

As more knowledge is gained about the mediators that play a role in the pathogenesis of psoriasis, more targeted therapies are becoming available.

TNF-α targeted therapies

As early entries into the world of biologics used in psoriasis, TNF-α inhibitors may not seem like new players. However, certolizumab, a pegylated TNF inhibitor initially approved for Crohn's disease and later psoriatic arthritis, is currently in phase 3 clinical trial for psoriasis and has shown an 83% PASI 75 response rate with no unexpected safety issues.[1] As a result of its pegylation, there may be less anti-drug antibody formation and, thus, lower rates of immunogenicity and loss of response than with the other TNF-α inhibitors.[2]

IL-23 targeted therapies

Ustekinumab, an inhibitor of the p40 subunit common to IL-12 and 23, was a later addition to the armamentarium of biologic therapies for psoriasis. New development efforts are focusing on agents that bind the p19 subunit, inhibiting only IL-23. Guselkumab is one such agent that has shown an 81% PASI 75 response rate at week 16.[3] Another anti-IL-23 agent currently in trial is tildrakizumab which has shown a 78% PASI 75 and 51% PASI 90 response rate at week 16.[4] The most common adverse events of both guselkumab and tildrakizumab have been nasopharyngitis and upper respiratory tract infections (URIs).[3,5] Lastly, the yet-to-be-named BI 655066 has shown an 87% PASI 75 and 58% PASI 90 response rate at week 12 with 33% of patients remaining clear after 66 weeks.[6]

IL-17 targeted therapies

Anti-IL-17 agents are the hot ticket in research and development right now, likely because all have shown at least an 80% PASI 75 response rate, as well as high rates of PASI 90 and 100. Secukinumab was a frequent topic of discussion at this year's AAD meeting. Approved in the U.S. in January 2015 for treating moderate to severe psoriasis, secukinumab is unique in that the label recommends a dose of 300 mg, but notes that 150 mg may be acceptable with the same cost for either dose. At 300 mg, secukinumab achieved an 82% PASI 75, 60% PASI 90, and 29% PASI 100 response rate at week 12; however, the efficacy was lower in patients with prior biologic exposure. Secukinumab also works quickly with a PASI 50 response seen within three weeks. Nasopharyngitis, headache, and diarrhea were the most common adverse events. Mild to moderate candida infections responsive to standard therapy, and self-correcting neutropenia were also seen.[7] Secukinumab is also effective for psoriatic arthritis with ACR (American College of Rheumatology) improvement scores of 20, 50, and 70 seen in 50%, 35%, and 19% of patients, respectively.[8]

Ixekizumab and brodalumab are IL-17 inhibitors currently in phase 3 clinical trials. At week 12, ixekizumab had an 89.1% PASI 75 and 35.3% PASI 100 response rate, with 77.7% of patients maintaining the response after 60 weeks. This medication has also been shown to work quickly with a significant difference from placebo by week 1, a 50% PASI 75 response by week 4, and a 50% PASI 90 response by week 8. At the higher dose, there was no loss of efficacy in patients with prior biologic therapy. Ixekizumab has also been shown to be very effective for scalp and nail psoriasis with complete

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resolution in some.[9] Brodalumab has shown an 83% PASI 75, 70% PASI 90, and 42% PASI 100 response rate by week 12. Similarly to ixekizumab, brodalumab is fast-acting, with results at 4 weeks and no loss of efficacy with prior biologic exposure. Response was maintained at 52 weeks, and scalp and nail psoriasis also improve.[10]

UPDATE: After this article was written, Amgen stopped development of brodalumab "based on events of suicidal ideation in the brodalumab program," according to a company statement.

Oral therapies

Apremilast is an oral PDE-4 inhibitor already approved in the U.S. and Europe for the treatment of psoriasis and psoriatic arthritis. At week 16, apremilast had a 33% PASI 75 response rate[11] and was effective for palmoplantar and scalp psoriasis with 65% and 41% of patients clear or almost clear, respectively.[12] Apremilast is also effective for nail psoriasis with 44.6% of patients with a Nail Psoriasis Severity Index (NAPSI) score of 50 at week 16.[12] A major benefit of apremilast is that there are no monitoring requirements. It should be noted that in patients with severe renal impairment, the recommended dosing schedule is once daily, rather than twice.[13] The most common adverse events were nausea, diarrhea, nasopharyngitis, and URIs.[11,12] The gastrointestinal side effects typically resolve over time and can be decreased by titrating the dose. Weight loss of up to 5% of baseline has been seen independently of the gastrointestinal effects. The incidence of weight loss does not increase with longer apremilast exposure.[14]

Tofacitinib is an oral JAK inhibitor currently approved in the U.S. and several other countries for the treatment of rheumatoid arthritis (RA) and in phase 3 trials for the treatment of psoriasis. Tofacitinib had a 59% PASI 75 and 39% PASI 90 response rate at week 16, and has also been shown to improve nail psoriasis. The most common adverse events were nasopharyngitis and headache. Other safety issues included hyperlipidemia, increased rate of serious infections (particularly reactivation of herpes zoster), and nonmelanoma skin cancer (NMSC).[15]

It was once thought that complete clearance of psoriasis was not a realistic expectation of treatment. However, the number (of patients) needed to treat (NNT) to achieve PASI 75 and 90 response rates continually decreases with each successive generation of biologic agents. Also, PASI 100 response rates are seen with some of the new therapies. Therefore, complete clearance can be a goal of psoriasis therapy.[16]

Safety profile of biologics

There are now multiple long-term safety reports of biologic agents used in the treatment of psoriasis. Many of these are reports from large, multicenter prospective registries, such as the Psoriasis Longitudinal Assessment and Registry (PSOLAR), evaluating the safety of systemic and biologic agents; OBSERVE-5, looking at the safety of etanercept; and ESPRIT, which is obtaining long-term safety data for adalimumab. To further these efforts, meeting attendees were encouraged to participate in the CORRONA Data Collection Program, a registry established by the National Psoriasis Foundation (NPF) and Corrona LLC, a rheumatology-led research company, aiming to contribute to the education and clinical knowledge of psoriasis.

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Infection

Data from PSOLAR have shown that, as a group, biologics do not increase the risk of infection compared to nonbiologic agents. However, when the biologics were broken down into different agents, higher rates of serious infection were seen in the infliximab (2.5%) and adalimumab (2%) groups than in those on etanercept (1.5%), ustekinumab (0.8%), or nonbiologic agents (≤1.3%).[17] There was not an increased risk of infection in patients on etanercept when compared to those on nonbiologics or phototherapy in OBSERVE-5.[18] The majority of patients in ESPRIT were free of serious infections with the rate of opportunistic infection <0.1%. Interestingly, the rate of serious infections was higher within the first year of treatment, but lower and stable in those who had been on the medication for more than a year.[19] Additionally, in a long-term safety report of adalimumab by Leonardi et al,[20]

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there was not an increased risk of serious infection over time and no patients died from serious infection.

Major adverse cardiovascular events

In early-phase clinical trials, a risk of major adverse cardiovascular events (MACE) was seen with ustekinumab, but larger trials have not shown this.[21] Analysis of the PSOLAR data did not show a statistically significant increased risk of MACE with any of the biologic agents.[22] In ESPRIT, most patients remained free of cardiovascular events with an incidence of <1%. Additionally, incidence rates of all cardiovascular events remained stable with varying durations of adalimumab exposure.[23]

Malignancy

In current analyses of the PSOLAR data, rates of malignancies (excluding NMSC) were comparable across the treatment groups (0.5 to 0.81%) with rates comparable to what would be expected in the general population.[24] OBSERVE-5 also showed that the rates of malignancies were not higher than expected relative to data from MarketScan, including lymphomas and NMSC.[18] In ESPRIT, most patients remained free of malignancy. NMSC was reported in 1.1% of patients with the incidence of squamous cell carcinoma (SCC) comparable to that of basal cell carcinoma. Melanoma was seen in 0.2%, lymphoma in <0.1%, and other malignancies in 0.9% of patients. The rate of malignancies remained stable for patients with varying durations of adalimumab exposure.[25] Leonardi et al[20] also saw a slight increase in NMSC (0.7 to 0.8%) in patients on adalimumab, but no increase in other malignancies.

In addition to the data presented from the various registries, Dr. John Koo of the University of California San Francisco presented results of a project looking at consistent, statistically significant adverse events in biologic agents in the treatment of psoriasis. Dr. Koo's lab found that consistently significant adverse events included injection-site reactions from etanercept and NMSC and URIs from adalimumab. Inconsistently significant events included SCC and headache from etanercept. There were no significant events from ustekinumab.[26]

The benefits of the biologic agents typically outweigh the risks. However, patients should still be warned of the potential for infection and instructed to stop the biologic agent until their infection has resolved. Similarly, the increased risk of NMSC and importance of ultraviolet light (UV) protection should be discussed. With the outstanding safety profiles of the currently available and commonly used biologic agents, there is no reason that patients should be under-treated.[26]

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Psoriasis comorbidities

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Psoriatic arthritis

Despite the prevalence of arthritis in psoriasis patients, many patients have undiagnosed psoriatic arthritis. Providers should ask about joint pain, stiffness, and swelling. Presenters stressed the importance of checking all joints, including those in the feet, as early diagnosis of psoriatic arthritis is critical due to the potential for disabling erosive arthropathy and permanent joint damage.

Cardiometabolic disease

An elevated risk of MACE has been observed in patients with severe psoriasis, possibly due to common inflammatory mediators, including IL-1 and TNF-α. Patients with psoriasis have been shown to have a greater burden of unstable non-calcified coronary plaques leading to a higher risk for myocardial infarction (MI).[27] However, there is conflicting evidence regarding the relationship between psoriasis and cardiovascular disease (CVD). A recent large, observational study by Parisi et al[27] reported that psoriasis did not increase the short-to-medium term (over 3-5 years) risk of MACE after adjusting for other risk factors, but the co-occurrence of inflammatory arthritis and psoriasis was an independent risk factor.[28] Although there is uncertainty regarding the

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exact relationship between psoriasis and CVD, there is little question that there is an increased prevalence of the metabolic syndrome in patients with psoriasis, with TNF-α also a mediator in the pathogenesis of insulin resistance. It is this coexistence with increased BMI, insulin resistance, and impaired HDL function that can confound the association between CVD and psoriasis,[28] as these disorders can independently contribute to the formation of coronary plaques.[27]

As many of the cardiometabolic variables associated with psoriasis are modifiable, it is imperative that patients be screened for risk factors. All patients should be screened at the age of 18; however, screening from the onset of disease should be considered, as early onset psoriasis may lead to an increased risk of CVD.[29] The NPF recommends that blood pressure, heart rate, and BMI be measured every two years, with fasting blood glucose and a lipid panel measured every two to five years, depending on additional risk factors.[30] If using the Framingham risk score to calculate the risk of 10-year major adverse cardiac events, an additional 6.2% should be added for psoriasis patients.[31] Each component of the metabolic syndrome should be treated to goal.[29]

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Kidney disease

Patients with severe psoriasis have a 2-fold increased risk in developing chronic kidney disease (CKD) independent of traditional risk factors with a 4-fold increase in going on to develop end-stage renal disease. Younger patients are at a higher risk of having CKD.[32]

Sleep apnea, pulmonary disease

A high rate of obstructive sleep apnea (OSA) has been reported in psoriasis patients; however, the analysis was not adjusted for risk factors of OSA including smoking and obesity.[33] In a study that did adjust for obesity, patients with OSA were found to have a 2.3-fold higher rate of developing psoriasis.[34] Thus, more studies are needed to determine the correlation between psoriasis and sleep apnea.

The adjusted risk of asthma and chronic obstructive lung disease (COPD) are 1.4-[35] and 2.4-fold[36] higher in patients with psoriasis, respectively.

Effect of biologic therapy on comorbidities

The effect of biologics on comorbidities is a growing area of interest, particularly CVD. Earlier studies in RA suggested that TNF-α inhibitors might reduce the risk of MI. Later psoriasis-specific studies supported this theory, reporting a slowed progression of atherosclerosis,[37] decreased aortic stiffness,[38] and a reduction in MI risk.[39] It should be mentioned that in addition to TNF-α inhibitors, methotrexate and phototherapy are also associated with a reduced risk of MACE,[39,40] although ustekinumab is not.[40] In a study by Abuabara et al, there was not a significant difference in the risk of MI between patients receiving systemic therapy and those receiving phototherapy after adjusting for cardiovascular risk factors.[41] In addition to the potential effect on CVD, TNF-α inhibitors have also been associated with lower diabetes risk.[42] While TNF-α inhibitors may reduce cardiometabolic disease, it is not recommended that these agents be prescribed specifically for this reason,[43] particularly as the cardioprotective effects of these medications are based on observational studies and more data are needed to show causality. Ongoing clinical trials are evaluating the impact of anti-inflammatory agents on vascular inflammation and cardiovascular risk in patients with psoriasis, with the aim of determining causality. We should see results in the near future.[21,27]

Phototherapy

Although the treatments for psoriasis are moving toward more targeted therapies, there was still a significant amount of discussion regarding traditional therapeutic approaches, including phototherapy. Phototherapy is an effective treatment modality for psoriasis, yet one to which dermatology residents have little exposure. Skin cancer in Caucasian patients is often the main concern with phototherapy. However, there is not an increased risk of skin cancer with UVB phototherapy[44] or topical PUVA (UVA in combination with the photosensitizing agent psoralen).[45] After more than 200 sessions, systemic PUVA has been reported to increase the risk of SCC and possibly melanoma.[44,45]

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Special populations

Pediatric patients

As a highly visible disease, psoriasis can have a profound emotional toll on psychosocial development in pediatric patients. An early age of onset may result in more severe disease over the course of a lifetime; thus, it may be prudent to be more aggressive with treatment in pediatric psoriasis.[46] While topical agents should be first-line, systemic agents may be necessary. Unfortunately, there are a limited number of clinical trials in pediatric patients especially for systemic therapies.

Etanercept has been shown to have a 57% PASI 75 response rate at week 12.[47] At this year's AAD meeting, Landells et al presented data from the CADMUS trial, a study evaluating ustekinumab in adolescent patients with psoriasis. At the standard dose, the study showed an 80.6% PASI 75, 61.1% PASI 90, and 38.9% PASI 100 response rate at week 12. There was also a good response to half the standard dose with a 78.4% PASI 75, 54.1% PASI 90, and 21.6% PASI 100 response rate, but the response was better-sustained over each dosing interval with the standard dose. The response was sustained through week 52 for both dosages and there were no new adverse events in the study population.[48]

Speakers were looking forward to the presentation of a trial comparing adalimumab and methotrexate in a pediatric population reported at the World Congress of Dermatology in June.

Infections

If topical steroids are inadequate, phototherapy, acitretin, and apremilast may be the most appropriate therapy options in patients with frequent or chronic infections.[49] Reactivation of hepatitis B infections has been reported with TNF-α inhibitors and the AAD, British Academy of Dermatology (BAD), and European guidelines recommend against using these medications in patients with chronic hepatitis B.[49] This is not the case with hepatitis C, as a randomized placebo-controlled trial concluded that etanercept decreases viral activity when used as an adjuvant therapy to interferon and ribavirin.[50] Therefore, the BAD and European guidelines allow for the use of etanercept in patients with hepatitis C if properly monitored, although this

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is not approved by the U.S. Food and Drug Administration (FDA).[49] Methotrexate, TNF-α, and IL-12/23 inhibitors are additional therapies that can be used in patients who have successfully been treated for tuberculosis.[49] As patients with HIV are already at an increased risk of infection, biologic therapy may be inappropriate. However, because TNF is thought to play a role in the progression of HIV, TNF-α inhibitors, particularly etanercept,[51] may be beneficial in HIV-positive patients, but this is not FDA-approved.[49]

Malignancy

Phototherapy, methotrexate, acitretin, and apremilast should be the next step in the treatment of topical steroid-refractory psoriasis in patients with a history of malignancy.[49] However, a history of malignancy is not necessarily an absolute contraindication to biologic therapy. While biologics should be avoided in active malignancy and lymphoma patients, five years of remission may be sufficient in other malignancies. Oncology should be involved and the probability of recurrence taken into consideration.[52]

Pregnancy

Although no studies have assessed the safety of biologic agents in the treatment of psoriasis during pregnancy, registry data have shown that patients who get pregnant on biologics have good outcomes. Despite this, the AAD, BAD, and European guidelines recommend that biologic therapies should be avoided in planned pregnancies. Narrowband UVB can be effective in patients without psoriatic arthritis, but cyclosporine may be necessary in those with arthritis, in which case, it is important to work in collaboration with the obstetrician.[49]

Elective surgery

Guidelines suggest discontinuing TNF-α inhibitors four half-lives prior to surgery; however, anecdotal evidence

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has shown that one to two weeks may be sufficient. These agents can be resumed one to two weeks after surgery, provided there is satisfactory wound healing and no evidence of infection.[49]

Vaccines

Inactivated vaccines are safe in patients on biologic agents, although the efficacy may be compromised. Live vaccines, however, are contraindicated and patients should wait four half-lives after stopping the medication before receiving a live vaccine,[49] and a period of at least two to three months should be allowed prior to resuming the agent.[52]

Genetics of psoriasis

Knowledge about the genetics of psoriasis is important for understanding disease mechanisms for new therapeutics and can be helpful in identifying disease subtypes to predict prognosis and response to therapy. There are now 45 known psoriasis genetic loci. Most of these are noncoding, regulatory single-nucleotide polymorphisms (SNPs), leading to a small increased risk of developing psoriasis; therefore, a combination is needed to cause the disease. Psoriasis genes cluster into the TNF-α/NF-κβ, TH17/IL-23, and antigen presentation pathways. Many of these genes are shared with other diseases, including CVD, with the FUT2, UBE2L, and SH2B3 genes common to these conditions. The age of onset is also associated with different pathways, with HLA-Cw6 and IL-22 associated with early onset psoriasis, ERAP1 associated with onset between 10 and 20, and IL-1β associated with onset after the age of 40.[53]

Pustular psoriasis

In addition to knowledge gained about the genetics of plaque psoriasis, more is now known about the genetics of pustular psoriasis. In patients with refractory generalized pustular psoriasis (GPP), deficiency of the IL-1 receptor antagonist (DIRA) and deficiency of the IL-36 receptor antagonist (DITRA) should be considered. Both are rare autosomal recessive diseases in which there is a severe pustular skin eruption; however, DIRA presents in infancy, while DITRA can present at any age. Not surprisingly, IL-1 receptor antagonists are effective in patients with DIRA and may also be effective in patients with DITRA. Mutations in the IL-36RN gene are not only seen in DITRA, but also in acrodermatitis continua of Hallopeau (ACH) and palmoplantar pustulosis (PPP). More recently, the AP1S3 gene was found to play a role in ACH, GPP, and less frequently PPP. Increased levels of IL-1 may also be seen in AP1S3 mutations.[54]

Whether PPP is a separate disease entity, or a variant of palmoplantar psoriasis, remains controversial. As in palmoplantar psoriasis, there is a higher incidence of PPP in women and a strong correlation with smoking. PPP has also been associated with thyroid disease, gingivitis, dental abscesses, and recurrent tonsillitis. For these reasons, it is suggested that thyroid stimulating hormone (TSH) be measured, smoking cessation be stressed, and tonsillectomy considered in these patients. In disease refractory to topical corticosteroids, second-line therapies include acitretin, phototherapy, cyclosporine, and ustekinumab.[55]

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TNF-α inhibitor-induced psoriasis was a topic of discussion. While these agents may induce PPP, in some cases they can be an effective treatment. Therefore, these agents should not be discontinued too hastily. Topical corticosteroids should be used and time allowed to see if there is any improvement. If the psoriasis persists, the anti-TNF-α agent should be discontinued. Anecdotal evidence has shown that switching within the class is usually ineffective, but ustekinumab and nonbiologic therapies may be beneficial.[55,56]

Summary

New and investigational therapies for psoriasis were main points of discussion at the 73rd annual meeting of the AAD. The safety profile of currently available biologic agents was also a frequent topic, and the interim reports of large patient registries are quite favorable. We can look forward

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to more data regarding the effect of psoriasis therapies on comorbidities, as well as effective therapies for pediatric psoriasis. As more advances are made in gene sequencing, we can expect a greater convergence of genetics and therapeutics. With all of the discoveries occurring in the field of psoriasis, there is great potential for decreasing the burden of this systemic disease.

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